having said malignant tumor, wherein said immunostimulatory dosage is about 500 U/m^2 to about 1,000,000 U/m^2 per day [or less].

26. (Twice Amended) A method for [treating] stimulating the immune system of a human patient having a non-resectable malignant tumor, said method comprising administering an immunostimulatory dosage of an α-interferon composition to said patient and treating said patient with effective non-surgical medical methodologies to diminish said tumor, wherein said immunostimulatory dosage is about 500 U/m^2 to about 1,000,000 U/m^2 per day [or less].

REMARKS

Claims 1-12, 15-16, and 18-26 are pending and stand rejected. Claims 15-16 have been canceled without prejudice to continued prosecution and claims 1-6 and claims 23-26 have been amended to recite a lower dosage of about 500 U/m^2 of α-interferon. Support for this amendment can be found throughout the specification, including, for example, at page 11, lines 16-17. Claims 1 and 23-26 have been amended to recite either a method for stimulating the immune system or that administration of an α-interferon composition is effective for stimulating the immune system. Support for these amendments can be found throughout the specification, including, for example, at page 8, lines 22-27 and at page 9, lines 21-29. Claim 23 has been amended to recite that the immunostimulatory dosage reduces post-operative infections in the patient. Support for this amendment can be found throughout the specification, including, for exmaple, at page 14, lines 18-20. No new matter has been added. Applicant respectfully requests reconsideration and allowance of claims 1-12 and 18-26 in view of the above amendments and following remarks.

Rejections under 35 U.S.C. §112, second paragraph

The Examiner maintained a rejection of claims 24 and 25 under 35 U.S.C. §112, second paragraph. The Examiner contended that "it is not clear how the immunostimulatory dosage of the alpha-interferon results in treatment of a patient having a malignant tumor. Thus, it is not clear what information is included in the label or package insert."

Applicant has amended claim 24 to recite that administration of α-interferon followed by surgical resection of a malignant tumor is effective for stimulating the immune system of a human patient having the malignant tumor and amended claim 25 to recite that administration of an immunostimulatory dosage of an α-interferon composition in conjunction with treating the patient with effective non-surgical medical methodologies for diminishing the malignant tumor is effective for stimulating the immune system of the human patient having the malignant tumor. Thus, amended claims 24 and 25 indicate that administering the α-interferon composition to a patient before surgical or non-surgical treatment of the tumor is effective for stimulating the immune system of the patient and are sufficiently definite under 35 U.S.C. §112, second paragraph.

The Examiner rejected claim 1 under 35 U.S.C. §112, second paragraph as "it is not clear how the recited method steps result in a treatment of a human patient." as "resection of the resectable tumor is already a treatment for a patient having a resectable tumor."

Applicant has amended the preamble of claim 1 to recite that the method is for stimulating the immune system of a human patient having a resectable malignant tumor. Thus, it is clear that the recited method step of administering an immunostimulatory dosage of α-interferon to the patient then surgically resecting the tumor results in stimulating the immune system of the patient. Applicant submits that amended claim 1 is sufficiently definite under 35 U.S.C. §112, second paragraph.

The Examiner rejected claims 1 and 23-26 under 35 U.S.C. §112, second paragraph, with respect to the use of "or less". Applicant has amended independent claims 1-6 and 23-26 such that the range 500 U/m^2 to 4,000,000 U/m^2 is recited as the immunostimulatory dosage. Amended claims 1 and 23-26 are sufficiently definite under 35 U.S.C. §112, second paragraph.

The Examiner rejected claims 1-7, 9-12, and 23-26 under 35 U.S.C. §112, second paragraph, with respect to the use of the term "about". Applicant respectfully traverses.

The term "about" is used to encompass experimental variability in measuring the units of the α-interferon composition. One of ordinary skill in the art would understand that two methods for assaying the α-interferon composition may result in units of activity that differ slightly from one another. Thus, claims 1-7, 9-12, and 23-26 are sufficiently definite under 35 U.S.C. §112, second paragraph.

The Examiner rejected claims 15 and 16 under 35 U.S.C. §112, second paragraph, "as it is not clear if the increase in T-lymphocyte activation or function is in addition to increasing the NK lymphocyte activity or instead of increasing NK lymphocyte activity." Applicant has canceled claims 15 and 16.

The Examiner rejected claim 15 under 35 U.S.C. §112, second paragraph, as "it is not clear how merely activating T-lymphocytes results in treatment of a patient as 'T-lymphocyte activation' appears to be functionally different from 'T-lymphocyte function'." Applicant has canceled claim 15.

The Examiner rejected claim 23 under 35 U.S.C. §112, second paragraph, as "it is not clear how the recited method steps result in preventing post-operative infection." The Examiner asserted that claim 23 is "lacking a correlative step that associates the preamble of the claim with the recited method steps."

Applicant has amended claim 23 to recite a method for stimulating the immune system of a patient prior to undergoing surgery. The method includes administering an immunostimulatory dosage of an α-interferon composition to the patient before surgery, wherein the immunostimulatory dosage reduces post-operative infections in the patient. Thus, amended claim 23 has a correlative step that associates the preamble of the claim with the recited method step.

The Examiner rejected claim 26 under 35 U.S.C. §112, second paragraph. The Examiner asserted that "it is not clear how the recited steps result in a treatment of a human patient having a non-resectable malignant tumor. Furthermore, it is not clear what is encompassed by 'effective non-surgical medical methodologies'."

Applicant has amended the preamble of claim 26 to recite that the method is for stimulating the immune system of a patient having a malignant tumor. It is clear from the amended claim that the recited step results in stimulating the immune system of the patient. With respect to the phrase "effective non-surgical medical methodologies", the specification provides radiation therapy as an example of a non-surgical methodology and a person of ordinary skill would have knowledge of other effective methodologies, such as chemotherapies.

In view of the above remarks, the Examiner is requested to withdraw the rejection under 35 U.S.C. §112, second paragraph.

Rejection Under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 15 and 16 under 35 U.S.C. §112, first paragraph. The Examiner asserted that "[t]he specification does not provide teachings or data indicating which types or if all types of T-lymphocytes are activated and exhibit increased functioning with the administration of α-interferon. Nor does the specification teach or disclose how increased functioning of specific T-cell types may be used in the claimed invention." Applicant has canceled claims 15 and 16.

The Examiner rejected claim 23 under 35 U.S.C. §112, first paragraph. The Examiner contended that "a little as a single round of multiplication of a single organism would constitute an 'infection'" and that "it is not clear from the specification how interferon may be used in a method for absolute prevention of an infection, given the broad definition of infection."

Applicant has amended claim 23 to recite that the immunostimulatory dosage reduces post-operative infections in the patient. The specification indicates that administering an immunostimulatory dosage to a patient prior to undergoing surgery can stimulate the patient's immune system prior to surgery. Stimulating the patient's immune system prior to the patient receiving a pre-surgical anesthetic can prevent post-operative suppression of the patient's immune system and reduce the risk of postoperative infection. See, specification at page 14, lines 12-20. The Examiner is requested to withdraw the rejection of claim 23 under 35 U.S.C. §112, first paragraph.

Rejections Under 35 U.S.C. §102(b)

The Examiner maintained a rejection of claims 24 and 25 under 35 U.S.C. §102(b) as being anticipated by Ucar et al. The Examiner asserted that "[f]or examination purposes, the label or package insert elements of the claimed articles of manufacture are considered to be intended use limitations." and cited MPEP §2111-02. The Examiner also alleged that the "information contained in the label or package insert does not clearly state that a specific dose is to be used and only states that administration of α-interferon 'can be' effective for treatment of a malignant tumor." The Ucar et al. reference was deemed to disclose three commercial preparations of α-interferon that are useful clinically.

Claims 24 and 25 have been amended to include a specific dosage range. The Ucar et al. reference does not disclose that administration of about 500 U/m^2 to about 4,000,000 U/m^2 per day or about 500 U/m^2 to about 1,000,000 U/m^2 per day of α-interferon followed by either surgical resection of a malignant tumor or non-surgical methodologies are effective for stimulating the immune system of a human patient having a malignant tumor. Thus, the label or package insert of amended claims 24 and 25 indicates a specific range of dosages can be administered to stimulate the immune system of a patient.

"Differences between an invention and the prior art cited against it cannot be ignored merely because those differences reside in the content of printer matter." In re Gulack, 217 USPQ 401, 403 (Fed. Cir. 1983). This is because describing an element as printed matter reveals nothing about the differences between an invention and the prior art. In re Gulack, 217 USPQ 399, 403 (Fed. Cir. 1983). Instead, "[t]he Patent and Trademark Office (PTO) must consider all claim limitations when determining the patentability of an invention over the prior art." In re Lowry, 32 USPQ2d 1031, 1034 (Fed. Cir. 1994). It is impermissible to dissect out elements of a claim and then declare the remaining portion of the mutilated claim unpatentable. In re Gulack, 217 USPQ 401, 403 (Fed. Cir. 1983).

As a result, proper analysis mandates that a claim be read as a whole. In re Gulack, 217 USPQ 401, 403 (Fed. Cir. 1983). Furthermore, ignoring a claim element simply because the element is unpatentable by itself "is no reason for ignoring it when the claim is directed to the combination." In re Miller, 164 USPQ 46, 49 (CCPA 1969). Indeed, a patentable invention comprises a combination of all new, partly new or all old elements. Rosemount, Inc. v. Beckman Instruments, Inc., 221 USPQ 1, 7 (Fed. Cir. 1984).

Thus, the content of the printed matter portion of the present invention must be considered in determining patentability. In the present case, it has not been established that the content of the printed matter in the claims, i.e., administrating immunostimulatory dosages of α-interferon (500 to 4,000,000 U/m^2 or 1,000,000 U/m^2 per day) followed by surgical resection or by non-surgical methodologies is effective for stimulating the immune system of a patient, is taught in the cited prior art. Thus, Applicant respectfully submits that the claimed combination is drawn to allowable subject matter. The Examiner is requested to withdraw the rejection under 35 U.S.C. §102(b) over the Ucar et al. reference.

The Examiner maintained a rejection of claim 26 under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 4,846,782 (the '782 patent). The Examiner alleged that it was not clear if about 1,000,000 U/m^2 was different from about 2,000,000 U/m^2. Applicant respectfully traverses.

As described above, the term "about" is used to encompass experimental variability in measuring the units of the α-interferon composition. One of ordinary skill in the art would understand that a difference in 1,000,000 U, however, is outside the range of experimental variability. The '782 patent does not disclose a method for stimulating the immune system of a human patient having a non-resectable malignant tumor that includes administering 500 U/m^2 to 1,000,000 U/m^2 of an α-interferon composition to the patient then treating the patient with effective non-surgical medical methodologies to diminish the tumor. In view of the above, the Examiner is requested to withdraw the rejection under 35 U.S.C. §102(b) over the '782 patent.

Rejection Under 35 U.S.C. §103

The Examiner maintained the rejection of claims 1, 7, 8, and 15-22 under 35 U.S.C §103 as being unpatentable over Markovic et al. in view of either Golub et al., Toliou et al., or Neefe et al., and also applied it to claims 2-6. The Examiner asserted that Applicant's arguments were not persuasive as "there are no teachings in Markovic et al. that would suggest that a maximum effective dose for mice had been found. Thus, the observation that the higher of two doses used in mice was more effective than the lower dose cannot be extrapolated to a conclusion that a reference teaches that ever increasing doses of an agent will always have a beneficial effect." Claims 15-16 have been canceled. Applicant respectfully traverses the rejection with respect to claims 1-8 and 17-22.

Independent claim 1 has been amended to recite that the immunostimulatory dosage is about 500 U/ m^2 to about 4,000,000 U/ m^2per day. The combination of Markovic et al. with either Golub et al., Toliou et al., or Neefe et al. does not teach or suggest a method of stimulating the immune system of a human patient that includes administering about 500 U/m^2 to about 4,000,000 U/ m^2 per day of α-interferon to the patient then surgically resecting the malignant tumor.

As indicated in MPEP § 2141, "the following tenets of patent law must be adhered to:

(A) The claimed invention must be considered as a whole;
(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention and
(D) Reasonable expectation of success is the standard with which obviousness is determined. Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986)."

Applicant disagrees that the teachings of the Markovic et al. reference provide the legally required reasonable expectation of success in stimulating the immune system of human patients by the method of amended claim 1.

The Markovic et al. reference administered $2.5x10^4$ U to $1.0x10^5$ U of α-interferon to mice with primary tumors prior to excision of the tumors. It was observed that tumor-associated mortality was limited and that administration prior to surgery was more effective than administration after surgery. The Markovic et al. reference, however, does not teach or suggest that about 500 U/m^2 to about 4,000,000 U/ m^2 per day of α-interferon are useful for stimulating the immune system of human patients.

One of ordinary skill in the art could not have predicted with a reasonable expectation of success the dosage ranges of about 500 U/m^2 to about 4,000,000 U/ m^2 per day of α-interferon for stimulating the immune system of human patients. The immune systems of mice and humans are significantly different. For example, in mice, the total leukocyte count is between 6 and $15x10^9$/liter, with lymphocytes outnumbering granulocytes (80% to 20%, respectively). In contrast, in humans, granulocytes outnumber lymphocytes (1.7 to 7.0 $x10^9$/liter vs. 0.9 to 2.9 x 10^9/liter, respectively). Thus, the relative percentage of circulating lymphocytes in mice is different from that of humans. See, "Research Animals in Medicine", October 2, 1973, DNEW Publication No. (NIH) page 306 (copy enclosed); and "Handbook of Laboratory Animal Management and Welfare", 1994; Oxford University Press, page 115 (copy enclosed). As α-interferon stimulates lymphocytes, and in particular natural killer lymphocytes (see, for example, specification at page 7, lines 24-25), differences in the relative percentage of circulating

lymphocytes can impact the dosage of α-interferon that would be administered to mice versus humans.

Furthermore, the basal metabolism of mice also is higher than that of humans, which also can impact calculation of dosage. For example, average heart rate/minute of mice is 310 to 840 and respiratory rate/minute is 60-220, whereas in humans, the average heart rate/minute is 60-100 and the respiratory rate/minute is 14-28. See, page 115 of "Handbook of Laboratory Animal Management and Welfare", *supra*; page 172 of "Essential Medical Physiology", 1992; Ed. Johnson, Raven Press (New York, New York) (copy enclosed); and page 426 of "Pathophysiology: Concepts of Altered Health States", 3rd Ed., Porth, J.P. Lippincott Company (Philadelphia, Pennsylvania) (copy enclosed). Thus, one of ordinary skill in the art could not predict the particular dosage of α-interferon to be used in humans with a reasonable expectation of success.

The Golub et al., Toliou et al., and Neefe et al. references do not remedy the deficiencies of the Markovic et al. reference. The Golub et al. reference administered α-interferon to patients with metastatic malignant melanoma for 42 consecutive days. The Toliou et al. reference administered interferon-α2b to patients with renal cell carcinoma prior to surgery and evaluated tumor sections for the number of natural killer cells. The Toliou et al. reference indicated that natural killer cell values after interferon administration may be of use for selecting patients for more aggressive therapies or as a way to monitor biotherapies. See, Toliou et al. reference, page 256. The Neefe et al. reference administered recombinant interferon-αA to colon or breast cancer patients and assessed natural killer cell activity and the inhibition of tumor growth. The Golub et al., Toliou et al., and Neefe et al. references do not teach or suggest that administrating about 500 U/m^2 to about 4,000,000 U/ m^2 per day of α-interferon to a patient having a resectable malignant tumor, before surgically resecting the tumor, is an effective method of treatment for a patient with a malignant tumor. In fact, Neefe et al. were unable to correlate natural killer cell activity and inhibition of tumor growth. See, Neefe et al., page 877, second column. The Golub et al. reference did not find any correlation between natural killer activity and clinical benefit of the interferon. Five patients benefited from the interferon therapy while four patients had an increase in tumor growth during the therapy. In both groups, equivalent increases in natural killer cell activity were observed. See, Golub et al., pages 708-709. Thus, the combination of

cited art does not render the presently claimed methods obvious. The Examiner is requested to withdraw the rejection of claims 1-8 and 18-22 under 35 U.S.C. § 103.

The Examiner maintained a rejection of claim 23 under 35 U.S.C. §103, as being unpatentable over Markovic et al. in view of either the Golub et al., Toliou et al., or Neefe et al. references.

Claim 23 has been amended to recite a method for stimulating the immune system of a patient prior to undergoing surgery. The method includes administering an immunostimulatory dosage of an α-interferon composition to the patient before surgery, wherein the immunostimulatory dosage is about 500 U/m^2 to about 4, 000,000 U/m^2 per day, and wherein the immunostimulatory dosage reduces post-operative infections in the patient. The combination of the Markovic et al. and Golub et al., Toliou et al., or Neefe et al. references does not teach or suggest administering 500 U/m^2 to about 4, 000,000 U/m^2 per day of an α-interferon composition to a human before surgery. The Markovic et al. reference indicates that natural killer cell activity induced with interferon prior to surgery is not altered by anesthesia. The Markovic et al. reference does not teach or suggest that particular dosages of α-interferon (about 500 U/m^2 to about 4, 000,000 U/m^2 per day) are effective for preventing post-operative infections in humans. As indicated above, one of ordinary skill in the art would not have a reasonable expectation of success in predicting that such a dosage would be effective for preventing post-operative infections. Golub et al., Toliou et al., and Neefe et al. are discussed above and also do not teach or suggest that particular dosages of α-interferon can be administered prior to surgery to prevent post-operative infection. In view of the above remarks, the Examiner is requested to withdraw the rejection of claim 23 under 35 U.S.C. § 103.

The Examiner rejected claims 1-6 and 18-25 under 35 U.S.C. §103 as being unpatentable over Lennard et al. (Br. J. Surgery, 72(10):771-776 (1985). The Examiner deemed the Lennard et al. reference to disclose that "surgical trauma has an immunosuppressive effects on surgical patients and to disclose pre-operative administration of interferon. The Examiner asserted that it would have been obvious to have made the claimed methods at the time the invention was filed, and that the specific dose range was within the skill of the ordinary artisan "to have determined effective doses that provided maximal immunostimulatory activity with the least amount of side effects." Applicant respectfully traverses.

The Lennard et al. reference measured circulating levels of lymphocytes, α-1 proteinase inhibitor (α-1-PI), α-2 macroglobulin (α-2-M), α-2 pregnancy-associated glyoprotein (α-2-PAG), and plasma suppressive activity (PSA) in patients both pre- and post-operatively. It was noted that post-operatively, the number of circulating lymphocytes decreased (except for B lymphocytes), α-1-PI and α-2-PAG levels rose, α-2-M levels decreased with major surgery, and PSA was increased. The Lennard et al. reference also noted "a potential role exists for the administration of alpha interferon as an immunoprophylactic."

The Lennard et al reference does not teach or suggest administering a dosage of about 500 U/m^2 to about 4, 000,000 U/m^2 per day of α-interferon and in fact, does not teach or suggest any particular dosage. Current protocols for α-interferon therapy also do not teach or suggest the particular dosage. A recent report by Kirkwood et al. evaluated high dose (20×10^6 U/m^2/day for 5 days/week for 10 weeks followed by $10 \times 20 \times 10^6$ U/m^2 for 48 weeks) and low dose protocols (3×10^6 U/day for 2 years) of interferon therapy in high-risk melanoma patients. See, Kirkwood et al., J. Clin. Onc., 18(12):2444-2458 (2000), copy enclosed). A significant relapse-free survival benefit was noted for patients receiving the high dose, but not the low dose of interferon. Neither treatment resulted in an increase in overall survival. Thus, current interferon protocols are geared to high dose interferon therapy and would not lead one of ordinary skill in the art to the particular dosage recited in the present claims. In view of the above, the Examiner is requested to withdraw the rejection under 35 U.S.C. §103.

CONCLUSION

Applicant submits that all of the claims are now in condition for allowance, which action is requested. The Examiner is invited to telephone the undersigned agent if it is felt that such would advance prosecution of the application.

Filed herewith is a Petition for Automatic Extension with the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 2/15/01

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